Cancel Claims 19 and 20.

Cancel Claims 27 to 29.

30. (Amended) In a method of administering a drug to a host in need of said drug, the improvement comprising:

administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug or a derivative thereof covalently linked, either directly or through an optional linking group, to a targeting moiety that is an intracellular biodistribution modulating protein.

Cancel Claim 35.

REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-8, 21-26, 30-34 and 36, the only claims pending and currently under examination in this application following entry of the above requested amendments.

Solely in order to expedite allowance of the present application, Claims 16 and 30, and the claims dependent thereon, have been amended to limit the claims to methods of specifically directing a drug to an intracellular space. Support for these amendments is found in the previously pending claims, e.g., Claim 24, as well as in throughout the specification, including page 18, lines 24ff. Attached hereto is a marked up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made".** As can be seen from the above remarks and the attached copy of the marked up claims, no new matter has been introduced to the application by the above amendments. As such, the Examiner is respectfully requested to enter the above amendments.

As indicated above, the above amendments have been made solely in order to expedite allowance of the present application. The above amendments should not in any way be construed as an agreement by the Applicants with the Examiner's position, and the Applicants expressly reserve the right to pursue claims of the original scope in one or more continuation applications.

In the Final Rejection, the rejection of Claims 16-36 under 35 U.S.C. §102 (b) as being anticipated by WO 95/10302 published application was maintained.

As amended, the claims are limited to methods of directing a drug to an intracellular space or site. The goal of the claimed methods is accomplished by limiting the bifunctional molecule to one in which the drug is conjugated to an intracellular protein binding member. As such, excluded from the claims are methods of directing a drug to an extracellular site, where the bifunctional molecule includes an extracellular protein binding member.

Turning now to the cited reference, the conjugates disclosed by the WO 95/10302 published application are conjugates of a first binding member and a second binding member, where the second binding member binds **to a long-lived blood component**, i.e., to an **extracellular protein** that is present in blood, e.g., albumin. Furthermore, the WO 95/10302 published application is explicitly directed only to methods of maintaining a drug in an extracellular space. In other words, the WO 95/10302 application is exclusively directed to methods of directing a bifunctional molecule to an extracellular space, and not to an intracellular space. Throughout the disclosure of the WO 95/10302 application, the target binding member is a member that binds to a long-lived blood component. As such, the WO 95/10302 published application does not teach or even suggest a method of directing a molecule to an intracellular space, much less by using a bifunctional molecule in which the ligand component of the molecule binds to an intracellular protein.

Because the WO 95/10302 published application fails to teach or event suggest a method of directing any molecule to an intracellular space, much less by administering the bifunctional molecule as one that includes a ligand component that binds to an intracellular protein, it clearly does not anticipate Claims 16-8, 21-26, 30-34 and 36, which claims include the limitation that

the methods are for directing a drug to an intracellular site and that the ligand bind to an intracellular protein.

As such, WO 95/10302 fails to anticipate Claims 16-8, 21-26, 30-34 and 36 under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Claims 16-36 were also rejected under 35 U.S.C. §102 (e) as being anticipated by U.S. Patent No. 5,843,440. This patent contains the same disclosure as the above discussed WO 95/10302 application. As such, for the reasons provided above, Claims 16-8, 21-26, 30-34 and 36 are not anticipated under 35 U.S.C. §102 (e) by U.S. Patent No. 5,843,440 and this rejection may be withdrawn.

Finally, the Examiner has maintained the rejection of Claims 16-36 under 35 U.S.C. § 103(a) as being obvious over either WO 95/10302 or U.S. Patent No. 5,843,440 in view of U.S. Patent No. 5,830,462, asserting that the only difference between the claimed methods and the primary references is the size of the bifunctional molecules, which element is made up by the `462 patent.

However, as pointed out above, the primary references are fundamentally deficient in that **they do not teach or suggest methods of directing a drug to an intracellular space by administering the drug as a bifunctional molecule that includes a ligand for an intracellular protein.**

In the Examiner's summary of what the `462 patent teaches, the Examiner makes a number of statements that indicate that the Examiner may have misunderstood the teaching of this reference. For example, the Examiner indicates at the bottom of page 5 of the office action that bifunctional molecules of less than 5 kd are taught in the `462 patent because this patent teaches chimeric fusion proteins of FkBP12 and a tryosine kinase, FK506 fused to a DNA binding domain. However, these are fusion proteins and, as such, have a molecular weight far in excess of 5 kD. The Examiner also finds a disclosure of targeting to specific locations by pointing to the teaching of targeting the chimeric proteins to particular locations. However, this

is targeting of chimeric fusion proteins already present in the host, not of a drug moiety administered to the host. There is no teaching in the patent of targeting the bifunctional inducers of dimerization to any particular location. Furthermore, the Examiner makes the statement that the `462 disclosure is directed to methods of modulating biodistribution of a drug. However, nowhere in the patent is the term "biodistribution" or an analogous word provided, because the patent is not directed to methods of modulating biodistribution, but to a much more complicated system of effecting a biological response.

Specifically, the cited supplemental 5,830,462 patent is directed to a system in which engineered chimeric fusion proteins present in a subject are brought together by an administered bifunctional chemical inducer of dimerization to cause a desired effect that only occurs when the two chimeric proteins are brought together. In the system disclosed in the `462 patent, the subject must be genetically engineered to include the chimeric fusion proteins that respond to the later administered bifunctional molecule inducers of dimerization.

As such, the purpose of the system of the `462 patent is completely different from the purpose of the primary references. While the primary references are directed to methods of anchoring a third molecule to a long-lived blood product by using a bifunctional molecule that includes a ligand for the long lived blood product and a ligand for the third molecule, the `462 patent is directed to methods of inducing dimerization of two chimeric proteins that are inside of a cell. As such, the two disclosures are directed to entirely different areas of a host, the first being directed to extracellular locations and the second being directed to intracellular locations.

Contrary to the Examiner's reading there is no motivation among the references for one to modify the primary references to target to an intracellular protein, because no utility do so is provided. It would defeat the purpose of the primary references to swap out the long lived blood component ligand and it would not accomplish the purpose of the secondary reference because such a substitution would not result in the desired dimerization of the chimeric proteins.

Accordingly, contrary to the Examiner's reading, one would not be motivated by the combined teaching of the references to produce bifunctional molecules as employed in the presently claimed methods, much less to practice the claimed methods.

Because the `462 patent fails to teach directing a drug to any location, much less an intracellular location, by administering it as a bifunctional molecule and the Examiner has only cited this patent for its teaching of small sized bifunctional molecules, this reference fails to make up the fundamental deficiencies in the primary references as discussed above. Accordingly, the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods.

Because the combined teachings of the WO 95/10302 or 5,843,440 references in view of the 5,830,462 reference fails to teach or suggest the claimed methods, Claims 16 to 36 are not obvious under 35 U.S.C. § 103 over these references and this rejection may be withdrawn.

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: 8-5-02

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

16. (Amended) A method for ~~modulating~~ directing the biodistribution of a drug to an intracellular space upon administration to a host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug or an active derivative thereof and a targeting moiety that is an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said bifunctional molecule has a modulated biodistribution upon administration to said host as compared to a free drug control;

whereby said biodistribution of said drug upon administration to said host is ~~modulated~~ directed to an intracellular space as compared to a free drug control.

Cancel Claims 19 and 20.

Cancel Claims 27-29.

30. (Amended) In a method of administering a drug to a host in need of said drug, the improvement comprising:

administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug or a derivative thereof covalently linked, either directly or through an optional linking group, to a targeting moiety that is an intracellular biodistribution modulating protein.

Cancel Claim 35.